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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,636	08/17/2000	David Lewin	15966-560(CURA-60)	5147

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	26

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,636	LEWIN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19,24* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647, Examiner Bridget E. Bunner.

Continued Prosecution Application

The request filed on 21 December 2001 (Paper No. 22) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/640,636 is acceptable and a CPA has been established. An action on the CPA follows.

Status of Application, Amendments and/or Claims

The amendments of 21 December 2001 (Paper No. 23) and 28 August 2002 (Paper No. 25) has been entered in full. Claims 1-56 are cancelled and claims 57-66.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 57-66 are under consideration in the instant application.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 57-66, drawn to a method of inhibiting differentiation of a stem cells comprising contacting the cells with an isolated polypeptide comprising an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 2 or 6, classified in class 435, subclass 377.

   II. Claims 57-66, drawn to a method of inhibiting differentiation of a stem cells comprising contacting the cells with an isolated polypeptide comprising an amino acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 4, classified in class 435, subclass 377.

   III. Claims 57-66, drawn to a method of inhibiting differentiation of a stem cells comprising contacting the cells with an isolated polypeptide comprising an amino

acid sequence having at least 80% sequence identity to the sequence of SEQ ID NO: 5, classified in class 435, subclass 377.

The inventions are distinct, each from the other because of the following reasons:

c. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different products, restriction is deemed to be proper because these products constitute patentably distinct inventions for the following reasons. Each of SEQ ID NOs: 2/6, 4, and 5 is a unique sequence, requiring a unique search of the prior art. Searching all of the sequences in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their separate search requirements, restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Greg Zinkl on 28 August 2002 a provisional election was made with traverse to prosecute the invention of Group II, claims 57-66, drawn to SEQ ID NO: 4. Affirmation of this election must be made by applicant in replying to this Office action.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF INHIBITING DIFFERENTIATION OF A STEM CELL BY CONTACTING THE CELL WITH HEMA2".

Claim Objections

5. Claims 57-62 are objected to because of the following informalities:

5a. Claims 57-62 recite non-elected groups.

5b. Claim 58 recites the term "having" in line 1, but should recite "has".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. Claims 57-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, claims 57-66 are directed to a method of inhibiting differentiation of a stem cell comprising contacting the cell with an isolated polypeptide comprising an amino acid sequence having at least 80%, 85%, 90%, 95%, or 99% sequence identity to the sequence of SEQ ID NO: 4. The claims also recite that the cell is mammalian cell, particularly mouse. The claims recite that the stem cell is a hematopoietic stem cell.

The specification at page 22, lines 24-25 outlines a prophetic procedure for inhibiting proliferation or differentiation of a cell and that the cell can be a hematopoietic cell or an

endothelial cell (pg 22, lines 24-25). The specification also discloses that the method includes contacting a cell with one or more of the HEMA polypeptides of the invention in an amount sufficient to inhibit proliferation or differentiation (pg 23, lines 1-3). However, the specification of the instant application does not disclose any methods or working examples that indicate inhibition of the differentiation of any specific type of stem cell (hematopoietic or neuronal) by HEMA2 (SEQ ID NO: 4) *in vivo* or *in vitro*. The disclosed method is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. For example, the prophetic example does not teach the skilled artisan the optimal dosage, duration, and mode of administration of HEMA2 consisting of SEQ ID NO: 4. Furthermore, the claimed method is unpredictable and complex wherein one skilled in the art may not necessarily inhibit differentiation of a stem cell as compared to controls. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of HEMA2 of SEQ ID NO: 4. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

Furthermore, although the specification teaches that derivatives or analogs of the nucleic acids or proteins include molecules comprising regions that are substantially homologous to nucleic acids or proteins by at least about 80%, 95%, 98% or 99% identity (80-99%) (pg 34, lines 18-26), the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any

given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997,

Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to determine the optimal dosage, duration, and mode of administration of HEMA2 (SEQ ID NO: 4) to inhibit differentiation of all possible stem cells, generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

7. Claims 65 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 65-66 recite the limitation "stem cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Ohneda et al. Immunity 12(20): 141-150, 2000.

Hollands, P. Int J Develop Biol 41(2): 245-254, 1997.

Lotem J et al. Oncogene 21(21):3284-94, 2002.

Graham, GJ et al. Int J Exp Pathol. 78(4):197-218, 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
November 13, 2002

ELIZABETH C. KEMMERER
PRIMARY EXAMINER